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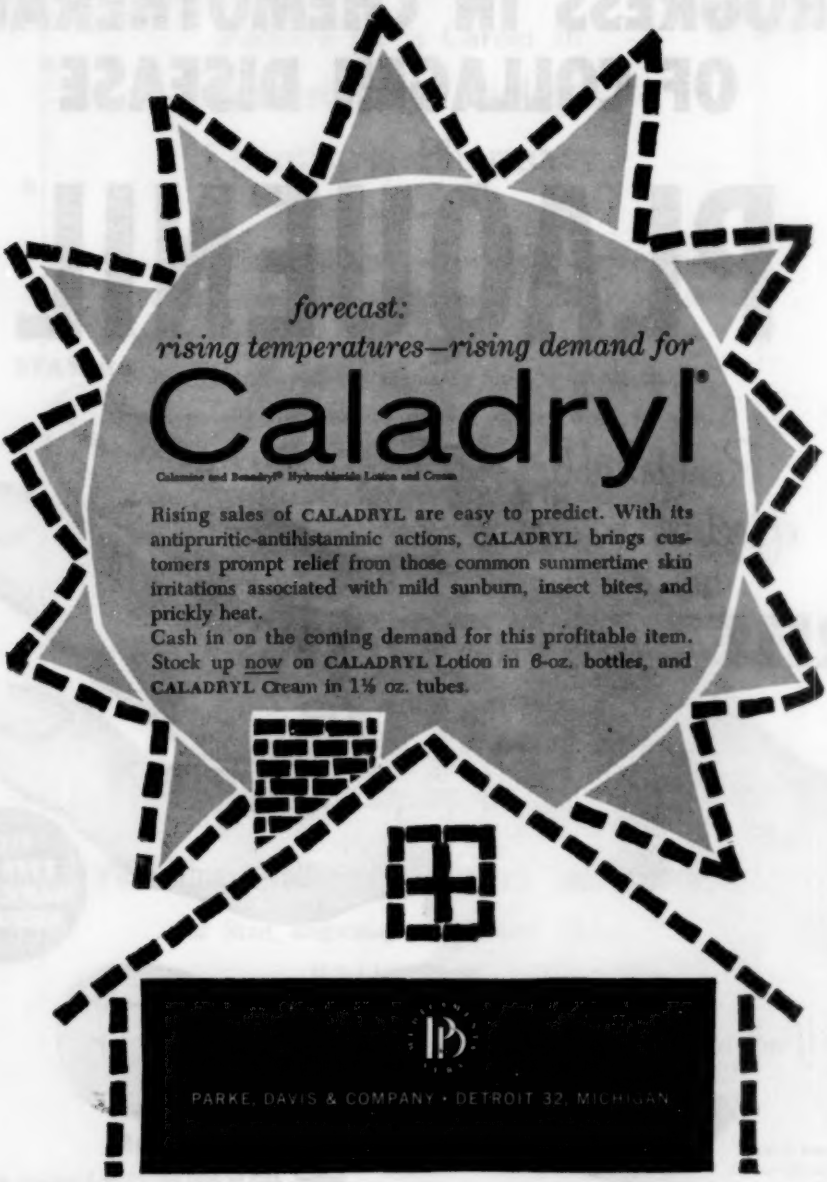
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EDITORIAL

INFLUENZA AND POLIO VACCINES

IN no field of production is obsolescence a greater factor to be reckoned with than in the manufacture of pharmaceuticals. It seems difficult to believe that less than a year ago the demand for Asian influenza vaccine was so great that it could not be bought by many who desired it at any price. Today, less than a year later, it is literally a "drug" on the market and one wonders how many millions of doses of it have been discarded since production overwhelmed the demand. Late last winter, it seemed that almost overnight the supply situation changed from one of great scarcity to that of over-abundance. Now, it is doubtful if there is any demand at all for this product and there probably will not be any in the future. The logical successor to this product is a polyvalent influenza vaccine containing, in addition to the Asian strain, all others which are known to cause this serious respiratory disorder.

It would be highly desirable if some active publicity and propaganda were directed toward the public with the objective of having this polyvalent vaccine used quite extensively, particularly by those who work and live in urban areas. Not only would its use reduce greatly the tremendous cost to industry of absenteeism by reason of illness, but it would undoubtedly save many lives among those whose general health is such that pneumonia as a complication is likely to follow the initial influenza. This risk is made even more serious by the increasing dissemination of resistant strains of *Micrococcus pyogenes* which can readily gain a foothold in the debilitated patient and result in a generalized infection, difficult or impossible to cure.

The situation with respect to poliomyelitis vaccine is somewhat analogous but quite different. Supplies of this are of such quantity that a considerable amount must be destroyed because it is outdated. Here, the overproduction is neither because of obsolescence nor because there is a better product for immunization. The reason is public apathy, in spite of the excellent statistical evidence that the use of

poliomyelitis vaccine has greatly reduced the incidence of paralytic forms of the disease and the death rate. It is hard to understand how parents of children who presumably love them can ignore the admonitions of the medical profession that they give their children the benefit of this protection. The product is available everywhere in the United States and at low cost; yet, right at this very moment, some father or mother is spending enough on cigarettes or beer to give their children this protection. This should not surprise those who have given some attention to the growing irresponsibility of Americans and their unwillingness to put first things first. The luxury items which they want, they are quite willing to buy—often at exorbitant prices and financed at relatively costly carrying charges. The things which are really important such as medical and dental care and education for their children, they feel the government should provide "free".

It sometimes seems that our government itself, or at least some branches of it, become a party to this faulty philosophy or help extend it by accusing the manufacturers of pharmaceuticals and the health professions of exorbitant profits and a total lack of concern for human welfare. The public is only too ready to believe these monstrous charges and, as is well known, the truth never catches up with a lie. It would be far better if the responsible persons in our state and national governments were to spend their time molding public opinion that health should be placed first and that the huge sums now being wasted by most families on unnecessary and costly gadgets could be better spent. It is, however, much more politically expedient to attack those who provide goods and services the public resents paying for and, thus, promote the thought that these should be functions of government. This is the ultimate aim of those who believe in state socialism and all of its implications, foreign though it is to our American way of life. Yet, the fact remains that nowhere in the world is America's production of drugs equalled or surpassed and it is our competitive system of free enterprise which gives us the advantage.

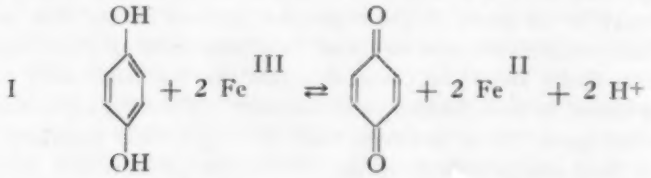
L. F. Tice

THE OXIDATION POTENTIALS OF ANTIOXIDANTS IN DRUG STABILIZATION *

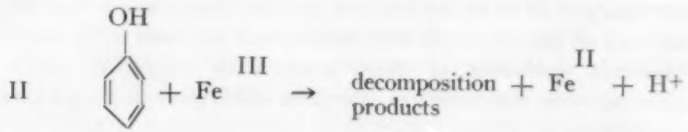
By Robert A. Nash †

MANY pharmaceuticals, today, are of complex molecular structure containing numerous functional groups, no one of which may be altered without forfeiting the inherent pharmacologic behavior. It is mandatory that antioxidants for the protection of pharmaceuticals, be judiciously selected with respect to compatibility and critically evaluated with respect to their relative effectiveness. A reliable and systematic evaluation of antioxidants has yet to be devised. It is the purpose of this paper to present the various techniques of determining redox potentials for antioxidants, to show the relationship of these potentials to antioxidant effectiveness, and finally to indicate their likely role in drug stabilization.

The Irreversible Oxidation Potential of Phenolic Antioxidants.— The determination of electrode potentials for organic compounds undergoing reversible oxidation-reduction was an established procedure prior to 1926. Unfortunately, many organic compounds, including most antioxidants and some pharmaceuticals, are oxidized irreversibly. Equation (I) is an illustration of a reversible reaction.



An irreversible reaction is illustrated in equation (II).



* Prize-winning manuscript in the Eastern Region, 1957 Lunsford Richardson Pharmacy Awards competition.

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Disregarding the effects of complex formation, the ferric ion is reduced to the ferrous oxidation state in both equations. The former establishes a reversible redox system with hydroquinone. The latter establishes an irreversible redox system with phenol.

In 1926, Conant and Pratt introduced the concept of the A. O. P.[1] In their study of the irreversible oxidation of several phenolic compounds, they defined the A. O. P. as the potential developed in thirty minutes by an equimolar ferri-ferrocyanide redox system in conjunction with the reduced phenol (1). In a subsequent study, Conant and Pratt reported A. O. P. values for a number of phenols, naphthols, and enols (2).

Four years later, Fieser introduced the technique of the discontinuous titration in order to obtain a more meaningful potential for unstable dihydroxyl phenols (3). Fieser was unable to obtain suitable E_0 values for monohydroxyl phenols because partial oxidation produced highly unstable free radicals. In a subsequent report he introduced E_c[2] value to replace the more unreliable A. O. P. (4). The velocity of the reaction between a phenol and a suitable reference redox system is shown as the ratio of oxidized to reduced form plotted against potential. An extrapolation to zero time yields a limiting value called the E_c. Unfortunately, the five reference redox systems employed only cover a limited range of potential, *i.e.*, from 600 to 1700 millivolts. E_c values were reported for more than seventy phenolic and amino compounds. Fieser devised a table showing the effect of ortho and para substitution on the E_c values for phenols and this table facilitated the calculation of potentials for many compounds without recourse to direct measurement.

For the next thirty years, the oxidation potentials of organic compounds were evaluated by either one of two procedures.

1. In the case of reversible compounds, a potentiometric titration was performed with an oxidizing agent. At fifty per cent oxidation, the ratio of the oxidized to reduced form becomes unity and knowing the standard potentials for the reference electrode and oxidizing agent, it is a simple matter to obtain E_0[3] values. Polarographic techniques also met with success because correlations between half-

[1] A. O. P. designates the term, Apparent Oxidation Potential.

[2] E_c designates the term, Critical Oxidation Potential.

[3] E_0 designates the term, Standard Oxidation Potential.

wave potentials and E_0 values are obtainable. The range, however, is limited to upwards of + 300 millivolts [4] due primarily to dissolution of the dropping mercury electrode.

2. In the case of irreversible compounds, the determination of the E_c values was possible, but the method proved lengthy and the results were considered mere approximations of the E_0 values. Thus, through this period, little was reported with Fieser's technique.

In 1953, Hedenburg and Gaylor both reported procedures for the anodic wave polarography of phenols (5, 6). Employing stationary micro-electrodes and automatic recording polargraphs, irreversible oxidation potentials were obtained by the former investigator with platinum and by the latter investigator with graphite anodes. The half-wave potentials evaluated could be determined in less time than with Fieser's technique. This procedure permits a table of potentials to be constructed for antioxidants whose overall oxidations are irreversible.

Antioxidants.—The rubber, petroleum, oil and soap industries have done the major portion toward the theoretical development and practical application of antioxidants. Today, antioxidants are designed to protect fats and oils from deteriorating in the presence of atmospheric oxygen over long periods of storage. However, it should be possible to apply the principles of antioxidant behavior in fats to the aqueous drug systems of pharmacy.

Shotton conveniently divided antioxidants into two categories (7).

1. The reducing agents. They are themselves oxidized by combining with any oxidizing agent present. Examples of these are the water soluble anions such as sulfite, nitrite, "Sulfinite" (8) and ascorbate.

2. "The True Antioxidants". They preferentially react with atmospheric oxygen thus protecting a compound from a similar reaction. Examples of these are the water insoluble ortho-, para-, di- and poly-phenols.

Table I shows a compilation of fat soluble antioxidants used in foods.

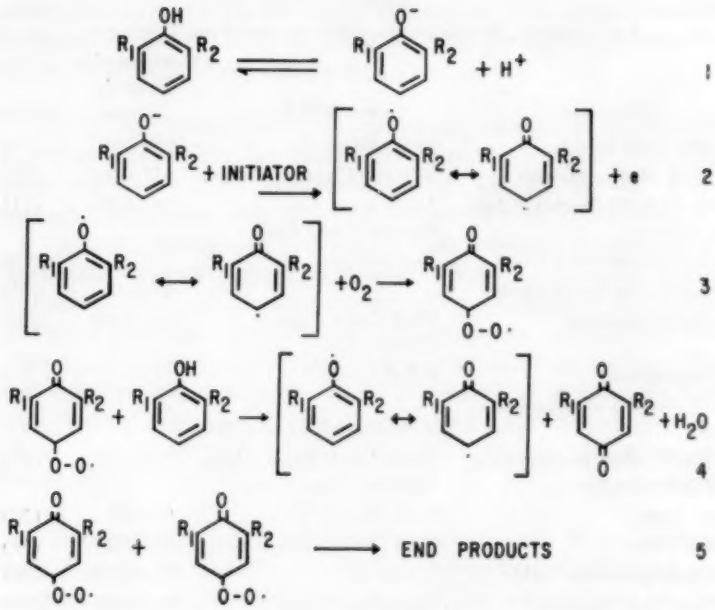
[4] Potentials are reported in the European sign convention *versus* a reference saturated calomel electrode having a potential of zero volts.

TABLE I

FAT SOLUBLE ANTIOXIDANTS USED IN THE FOOD INDUSTRY

Compound	*Commercial Source*	*Concentration Range in Percent*	*Reference*
Ascorbic Acid Esters	Chas. Pfizer Co.	0.06-0.03	(9)
Butylated Hydroxyanisole	Eastman Chem. Prods. Inc.	0.01-0.005	(10)
Caffeic Acid, Hydrocaffeic Acid (as Esters)	Lever Bros. Co. General Foods Corp.	0.05-0.006	(11)
Catechol Monododecyl Ether	DuPont Co.		(12)
Alpha and Beta Conidendrols		0.1-0.01	(13)
Di*tert*butylparacresol	Shell Chem. Corp. Koppers Co.	0.02-0.001	(14)
Di*tert*butylphenol	Ethyl Corp.		
N,N′-diphenyl p-phenylenediamine	B. F. Goodrich Chem. Co.		
Gallic Acid, ethyl, propyl, lauryl, and dodecyl esters	Goldschmidt Chem. Corp. Heyden Chem. Corp.	0.01-0.02	(15)
Guaiac Gum	S. B. Penick & Co.	0.1-0.01	(16)
Lecithin Conc.	A. E. Staley Mfg. Co.	0.1-0.005	(17)
Nordihydroguaiaretic Acid	J. Stange Co.	0.01-0.05	(18)
3,5-Pentadecyl Resorcinol	Gen. Foods Corp.	0.01-0.05	(19)
Sesamol		0.1-0.01	(20)
2,2′,3,3′-tetrahydroxy 5,5′ dimethylbiphenyl		0.005	(21)
Tocopherols, Hydroxychromans, Hydroxycoumarans	Distillation Prods. Hoffman LaRoche and Co.	0.1	(22)

It is generally agreed, that the mechanism for antioxidant action proceeds through an intermediary free radical formation (23). The following steps are proposed to explain the action of a typical substituted phenol as the sole antioxidant.



Step one shows the ionization of the phenol under proper conditions to produce a phenoxyl ion. The irreversible oxidation of the ion to a stablized free radical intermediate is indicated by the work of Campbell in step two (24). This reaction may be initiated by the solution and/or its environment. The attack of atmospheric oxygen on the free radical forms a stable peroxyl free radical illustrated in step 3. The propagation of step 4 repeats the chain through steps 2 and 3. Termination in step 5 is accomplished when all the oxygen is depleted. The more steric hindrance introduced into the antioxidant molecule, the more reluctant that molecule is to undergo side reactions in favor of the oxygen attack. This is evidenced by the fact that phenol itself is a poor antioxidant while the more sterically hindered di*tert*butylparacresol, for example, is not.

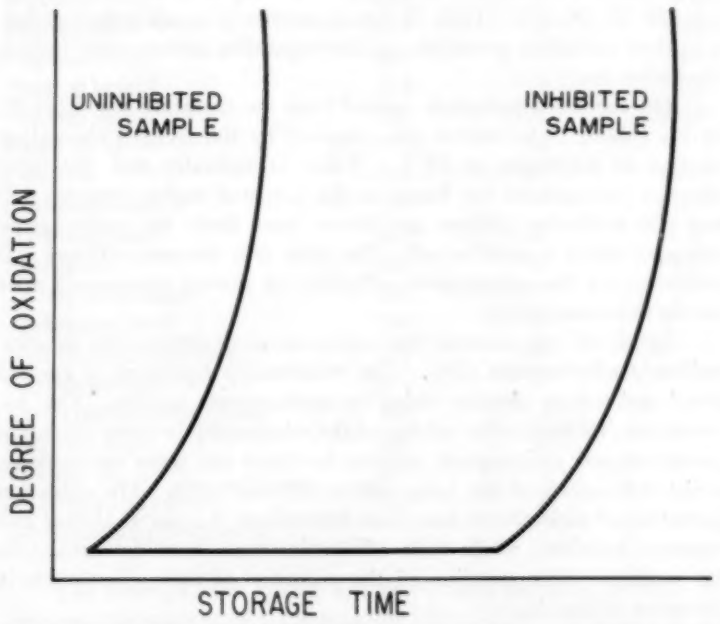
Di- and poly-basic acids should be mentioned here for their reinforcing action on phenolic antioxidants. Mattill designated them as synergists because of this effect. They are presumed to act as antioxidant regenerators by donating hydrogen to the oxidized antioxidant. Another view holds that these synergists are mild chelating

agents acting by complex formation with the antioxidants (25). Examples of these are phosphoric, tartaric, citric, succinic and malonic acids and their acid salts.

Methods for evaluating the efficiency of antioxidants in nonaqueous systems are covered adequately in the following references (26, 27, 28, 29, 30, 31, 32). In general, the means of determining the efficiency of antioxidants in nonaqueous media are similar to one another. A given concentration of antioxidant is added to the substrate[5] and permitted to stand at elevated temperatures for varying periods of storage. A plot of storage time vs. some function of the substrate's degree of oxidation is made as illustrated in Figure 1.

FIGURE 1

OXIDATION CURVES FOR THE DETERMINATION OF ANTIOXYGENIC EFFICIENCIES



[5] The substrate is defined as a labile compound which is prone to atmospheric oxidation.

The period of time from the initial introduction of the antioxidant to the first measurable degree of oxidation is termed the inhibition or protection time of the substrate. A similar curve for a substrate without the antioxidant added yields a negligible inhibition period. The ratio of inhibited to uninhibited sample times gives an index for the antioxygenic [6] efficiency under a given set of conditions. In general, the degree of oxidation in the nonaqueous substrate can be represented by either the percent of unsaturated bonds destroyed or the amount of oxygen absorbed by the substrate. Various investigators have so far been unable to apply antioxygen efficiency indices obtained on one fat substrate to other substrates, or to correlate the results obtained in one analysis with other analytical procedures. At the present time, it is difficult to propose reasons as to why these correlations have failed.

The Oxidation Potential and Antioxidants.—Golumbic and others have attempted to correlate antioxygenic activity with oxidation potential (28, 33, 34, 35). Table II lists a number of compounds together with their oxidation potentials and corresponding antioxygenic indices or efficiencies.

The oxidation potentials derived from the literature are either E_c or E_0 values. The indices are obtained by the oxygen absorption method in substrates at 75°C. Table II indicates that the most effective antioxidants are found in the potential region between 450 and 920 millivolts. Above and below these limits the antioxygenic efficiency index is small or nil. The peak falls between 600 and 800 millivolts but the antioxygenic efficiency of several compounds does not fit this relationship.

Egloff did not contend that oxidation alone determined an antioxidant's effectiveness (34). The relationship represents a general trend and not an absolute value for antioxygenic activity. One investigator still doubts the validity of the relationship between oxidation potentials and antioxygenic activity for there are some antioxidants which fall outside of the range 450 to 920 millivolts. The oxidation potentials of antioxidants have been determined in aqueous alcohol and aqueous solutions, while their efficiencies have been determined in fat systems. The question of the accuracy of their correlation is therefore debatable.

[6] For the purposes of this report, the word antioxygenic refers to the broader term antioxidative.

TABLE II

THE CORRELATION OF ANTIOXYGENIC ACTIVITY WITH OXIDATION POTENTIAL

Compound	Oxidation Potential millivolts [7]	Index in Lard 75°C (28)	Inhibition min. (34)
p-Nitrophenol	1433		45
Aniline	1135		60
Phenol	1089	1	60
m-Cresol	1080	1	90
Vanillin	1080		
Resorcinol	1043	1	135
o-Cresol	1040	1	120
p-Cresol	1038	1	163
*Beta*naphthol	1027	2	255
Eugenol	831		150
Phloroglucinol	813	3	75
*Alpha*naphthol	797	22	1920
Gallic Acid	799	18	
Catechol	768	41	1890
p-Aminophenol	703		1470
Hydroquinone	673	38	135
Pyrogallol	661	60	1440
Toluhydroquinone	656	7	
*Alpha*tocopherol	684	3	
Hydroxyhydroquinone	601	60	
Naphthotocopherol	573	6	
1,4-Naphthohydroquinone	484	2	
Ascorbic Acid	390	1	
Vitamin K	363	1	
2-Methyl-3-Hydroxy 1,4-Naphthohydroquinone	299	1	

The Concept of a Poised System.—Clark, as early as 1924, introduced the concept of poising action (36). It is comparable to the

[7] The oxidation potentials represent either E_c or E_0 values.

buffering action in an acid-base system. A solution may be said to be poised when it tends to resist changes in potential on the addition of an oxidizing or reducing agent. The redox potential of a poised system is analogous to the pH value of a buffered system.

A system with a ratio of (1:1), *i.e.*, oxidized to reduced form has the largest capacity to resist changes in potential and its ability to be displaced by oxidation is diminished. If an oxidation potential can be ascertained for a labile drug system, then the system can be poised or the potential stabilized by one of two methods. Either it can be poised at its own oxidation potential, which would be more acceptable to pharmacodynamicists, or it can be poised in the optimum potential range shown in Table II. Thus, a poising and buffering system might be developed with one or more antioxidants and synergists. An extensive research for antioxidants applicable to aqueous systems might include such compounds as amines, amino acids, thiols, and redox systems, as well as some preservatives and vitamins.

Drug Stabilization With Antioxidants.—The attempt thus far has been to consolidate the fields of irreversible oxidation potentials and antioxidants to drug stabilization. The literature of antioxidants, as applied to drug stabilization, is scant. For many years, the protection of medicinal agents against loss of therapeutic effectiveness by oxidation was all but ignored. In those instances where deterioration was obvious but not understood, little more was done other than storing in a cool, dark place and in well filled, tightly stoppered containers. In a few cases, where preservation could be rationalized on the basis of familiar chemical reactions, water soluble antioxidants were added on an empirical basis with varying degrees of success. Most of them are reducing agents acting in buffered media. Table III lists the more important ones.

TABLE III

WATER SOLUBLE ANTIOXIDANTS USED IN THE DRUG AND COSMETIC INDUSTRY

Compound	System Protected	Concentration Percent	Reference
Ascorbic Acid and Sodium Salt	Epinephrine Physostigmine		(38)
Cysteine Hydrochloride	Ascorbic Acid	0.1	(39)
Dihydropyrogallol			(40)
Hypophosphorous Acid	Ferrous Iodide	0.5	
Phenylalanine Sodium Nitrite	Epinephrine		(41)
Sulfites, Bisulfites, Metabisulfite Salts	Epinephrine Procaine, Morphine Pontocaine	0.1 to 0.01	(42)
Sulfinic Acid and Propyl and Butyl Esters	Epinephrine	0.1	(8)
Thiodiproprionic Acid and Esters		0.01	
Thioglycollic Acid			
Thiolactic Acid	Ascorbic Acid	1.2	(39)
Thiourea		0.85	(39)
Vitamin K			(43)

The sulfites are the most widely used in practice. In alkaline media they effectively combine with molecular oxygen and act like "True Antioxidants." The sulfites probably protect by a preferential oxidation to the sulfate state. They are undesirable for the following reasons:

1. They adsorb on rubber closures (37).
2. They introduce objectionable tastes to preparations.
3. They "breathe through" polyethylenes.

4. They are unstable in acid media.

5. They produce irritation at the sites of parenteral injections.

In his series, *Redox Systems in Pharmacy,* Dolder indicated the importance of selecting stabilizers with the proper redox potentials (39). His systems for stable epinephrine and ascorbic acid solutions incorporate the following features:

1. The replacement of the oxygen atmosphere with nitrogen or carbon dioxide.

2. The removal of trace metal ion catalysts through chelation. The Versenes [8] have been applied in this capacity with success (44).

3. The control of pH in obtaining optimum stability with suitable synergistic buffers.

4. The reduction in the deleterious effects of light and heat by employing suitable containers and handling procedures.

Although Dolder was not the first to demonstrate the effects of oxygen, trace ions, pH, light and heat on oxidizable systems, he did indicate the inherent difficulties in the determination of redox potentials for complex drug systems.

Conclusions

In conclusion, the future investigation of antioxidants in drug stablization and preservation should be concerned with the following factors.

1. More fundamental investigation is needed in the field of redox potentials. The technique for studying antioxygenic efficiency are still in their formative stages.

2. The number of natural and synthetic antioxidants of low order toxicity is quite small. The synthesis of tailor-made water-soluble phenols would extend the range of potentials for poising.

---

[8] A trade name for Dow Chemical Company's brand of salts of ethylenediamine tetracetic acid.

3. Factorial experiments for the evaluation of antioxidants by themselves and in drug systems need to be run. Such variables as levels of activity, solvent system, pH and potential should be included. Successful systems could then be subjected to the usual air, heat and light exposure tests.

The role of antioxidants has been established in connection with numerous industrial products but their future success in drug stabilization depends upon extensive research.

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STUDIES OF THE GENUS THYMUS
PART V

Comparison of the Diagnostic Microscopical Characteristics of Thymus carnosus Boiss. and Thymus villosus Linn.

By Ikram Hassan * and M. S. Dunn **

THIS paper is a report of our microscopical findings in the studies of Thymus carnosus Boiss. and Thymus villosus Linn. and is a continuation of our systematic coverage of the comparative histological structures of the Thymus species mentioned by Bailey (*2*).

Seven samples of T. carnosus Boiss. and three of T. villosus Linn. were studied from the following authoritative sources: Herbaria of the Philadelphia Academy of Natural Sciences, Botanical Garden of the University of Montreal, Harvard University, Munich Botanical Garden; United States National Herbarium; Baily Hortorium; and Conservatoire et Jardin Botaniques, Geneva.

As in other studies, the material used although obtained from herbarium sheets containing specimens either collected by or identified by recognized plant taxonomists, was still compared for authenticity with the descriptions given by Bailey (*2*) and Engler and Prantl (*3*).

Methods of Study

The method used in the present studies was the same as that reported in our paper (Hassan and Dunn (1)).

Summary

Of all our histological findings, the following were selected as most noteworthy:

I. The comparison of the palisade numbers of Thymus carnosus based on an average of 16 counts and of Thymus villosus on an average of 12 counts did not seem to be of value in the separation of these

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species. The palisade number of T. carnosus averaged 9.9 while that of T. villosus was 9.3.

II. The determination of the average number of stomata of the lower epidermis of the floral leaf per central square of the Howard micrometer ruling was practical only in case of T. carnosus. The leaf of T. villosus was palmately cleft, and the stomata were not uniformly scattered all over the surface. They were more numerous in the divided region of the leaf. Thus the stomatal average was not considered of significance. The average value for T. carnosus based on 16 counts was 9.5.

III. A comparison of the principal histological differences of the two species is given below:

A. Floral Leaf:

1. The upper epidermis in Thymus carnosus showed cells with extremely thick (but unlignified), and short walls with unstriated cuticle. The cell walls had a tendency to show beading here and there. The middle lamella of the cell walls was visible by use of the phase microscope. The stomata were absent. The cells of the epidermis gradually became wavy-walled in surface view in the petiolar region (Fig. I, 1). The cells of the upper epidermis in the case of Thymus

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FIGURE I.

Thymus carnosus Boiss.

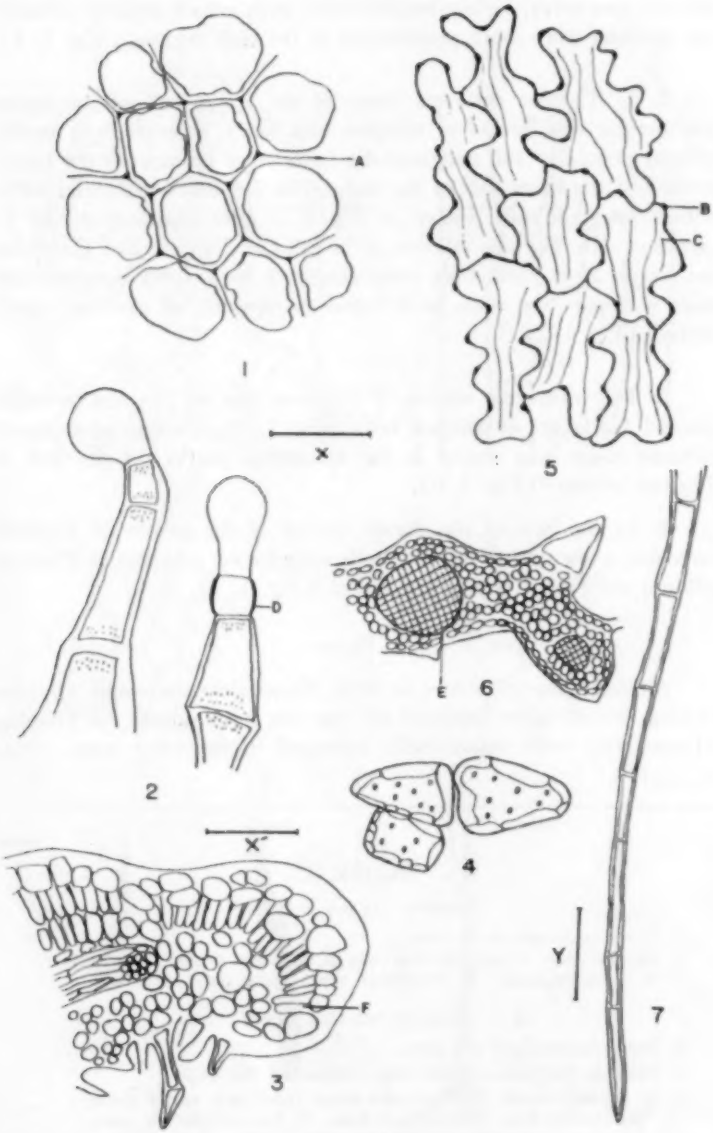
1. Upper epidermis of the floral leaf showing thick walls.
2. Glandular hairs with stout stalks.
3. Transverse section of the leaf.
4. Stone cells from the petiolar region of the leaf.

Thymus villosus Linn.

5. Upper epidermis of the floral leaf showing wavy walls.
6. Transverse section of the leaf.
7. Long nonglandular hair from the leaf.

A. middle lamella of the cell wall. B. beaded cell wall. C. cuticular striations. D. thick walled cell of the stalk. E. transversely cut vein of the leaf. F. palisade cell.

All drawings made with the aid of camera lucida. Scale X-34 microns for drawings 1, 2, 4, and 5. Scale X'-100 microns for drawings 3 and 6. Scale Y-150 microns for drawing 7.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villosus had wavy, lightly-beaded walls with cuticle scantly striated, and stomata were more pronounced in the cleft regions (Fig. I, 5).

2. In Thymus carnosus, most of the apical half of the upper leaf surface was devoid of nonglandular hairs, whereas both multicellular glandular and nonglandular hairs were present on the upper surface of the basal half of the leaf. The 2-4 celled glandular hairs with stout stalk cells, shown in Fig. I, 2 were characteristic of T. carnosus. In Thymus villosus, although the 2 to 4-celled glandular hairs with stout stalk cells were absent, 1 to 8-celled nonglandular hairs with papillose walls were found infrequently all over the upper surface (Fig. I, 7).

3. The transverse section of the floral leaf of Thymus carnosus showed 1-2 layers of palisade cells (Fig. I, 3), whereas pronounced palisade tissue was absent in the transverse section of the leaf of Thymus villosus (Fig. I, 6).

4. At the base of the dorsal surface of the petiole of Thymus carnosus, a few groups of stone cells were found, whereas in Thymus villosus such stone cells were absent (Fig. I, 4).

B. Stem:

Although the trichomes in both Thymus carnosus and Thymus villosus tended to be scattered all over the stem surface, in Thymus villosus they were occasionally arranged in imperfect rows (Fig. II, 1, 4).

FIGURE II.

Thymus carnosus Boiss.

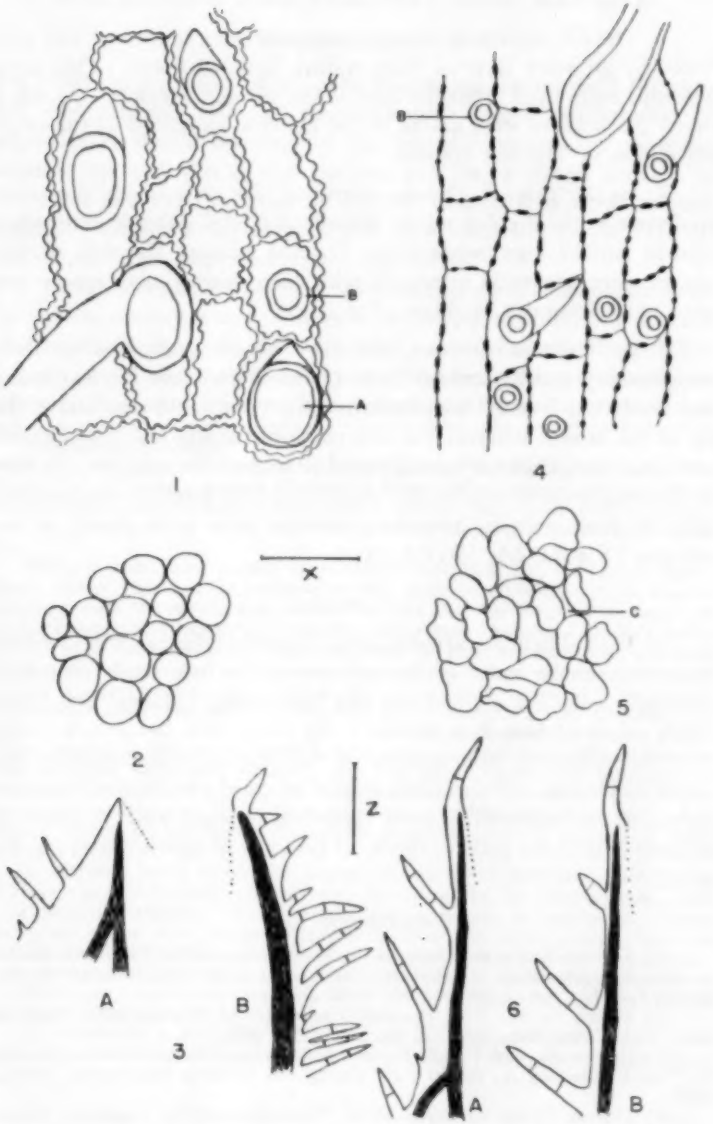
1. Outer epidermis of the stem.
2. Surface view of palisade-like cells of the outer region of the calyx.
3. A. Broader sepal. B. Narrower sepal (each only partly shown).

Thymus villosus Linn.

4. Outer epidermis of the stem.
5. Palisade-like cells of the outer region of the calyx.
6. A. Broader sepal. B. Narrower sepal (each only partly shown).

A. papilla-like hair. B. trichome scar. C. intercellular air space.

All drawings made with the aid of camera lucida. Scale X-34 microns for drawings 1, 2, 4 and 5. Scale Z-300 microns for drawings 3 and 6.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C. Calyx:

1. The rib regions of Thymus carnosus were supported and protected by an outer layer of thick walled, lignified fibers. This layer was uniformly thick from the base to the divided region of the calyx tube. Such fibers were absent in the material examined of the calyx rib region in Thymus villosus.

2. In the case of Thymus carnosus, the cells under the outer epidermis in the divided region resembled typical palisade cells when seen in surface view, whereas in Thymus villosus, the cells of this region were unequally arranged, with large intercellular spaces and were more irregular in shape (Fig. II, 2, 5).

3. In Thymus carnosus, the three broad sepals had on their margins very small glandular hairs (1-celled head and 2-celled stalk) and rarely 1 to 2-celled nonglandular hairs (not found near and at the tip of the sepal), whereas the two narrower sepals had 1 to 3-celled very stout nonglandular hairs situated all around the margins. In case of Thymus villosus, all the five sepals had 1 to 4-celled nonglandular hairs on their margins and the glandular hairs were absent on the margins (Fig. II, 3A, 3B; 6A, 6B).

D. Corolla:

In both Thymus carnosus and Thymus villosus, long 1-celled trichomes on the inner surface of the corolla tube with irregularly shrunken walls but without peg-like projections (Hassan and Dunn (4)), occurred here and there.

The following combination of histological characteristics not found in Thymus villosus Linn. should be noted for Thymus carnosus Boiss.: 1. extremely thick outer epidermis in floral leaf. 2. presence of stone cells in the petiole region. 3 presence of lignified fibers in the calyx.

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ALKALOIDS AND THE WITCHES' SABBAT

By George N. Conklin *

DESPITE a number of scientific caveats on the subject,[1] the general attitude (one all too frequently found, incidentally, in otherwise reputable histories of the period) toward the *mirabilia* reported by both the legal examiners and the wretched accused in witchcraft trials of the sixteenth century is simply to attribute such testimony wholly to superstition and naive credulity in the first instance and to prolonged torture in the second.[2]

To the uninformed layman, for example, such an explanation of the supernumerary witch's teat or extra nipple to nurse the familiar would quite likely (and understandably) seem the only one possible to account for such arrant nonsense. The fact that polymastia and polythelia [3] are not unknown and, according to some,[4] not even rare

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1. See, for instance, Margaret Murray's pioneer anthropological study, *The Witch-Cult in Western Europe*, Oxford U. Press, 1921; Langdon-Brown's *From Witchcraft to Chemotherapy*, Cambridge U. Press, 1941; Oesterreich's *Demoniacal Possession*, N. Y. 1930; and more recently Hughes' *Witchcraft*, London, 1952.

2. An attitude based largely upon antimediaevalism: i.e., the age of superstition, rather than a close scrutiny of the evidence. (Witchcraft is usually associated with the middle ages despite the fact that the witch terror began in the renaissance and lasted well into the seventeenth century). Lecky's influential *Rise of Rationalism in Europe* and even the great scholarship of Lea both suffer from this presumption. As an example of the lack of caution in statistical generalizations one need only observe the corrective criticism of Kittredge in his *Witchcraft in Old and New England* of R. Steele's *Social England*. In Steele's book it was flatly stated that under James I's revision of the Elizabethan Statute on Witchcraft 70,000 persons were executed up to 1680. Kittredge observed, after exhaustive research, that "no records have been published or examined which would justify the assertion that *one seventieth* part of this monstrous number met their death in the period named." Kittredge's own diligent search for executions during the reign of James I brought to light less than forty.

3. Although much rarer than polymastia, the strict definition of polythelia of Deaver and McFarland (*The Breast: Its Anomalies, Its Diseases and Their Treatment*, Philadelphia, 1917) is interesting in respect to polymastia. These authorities argue that because wherever a bona fide nipple occurs—even of rudimentary development—some mammary gland tissue is present, it is accordingly correct to call all cases of supernumerary nipple polymastia except those in which such a supernumerary structure is present upon what appears to be a single and otherwise normal mammary gland.

4. Polymastia is described by Deaver and McFarland (*op. cit.*) as a common congenital malformation. For statistical instances they cite amongst others

in modern clinical observation of course suggests the obvious reporting of observed cases on the part of the renaissance examiners as against what must seem the more plausible lie resulting from the fear and hysteria of the witchcraft terror.

So, too, with the witch's alleged insensitivity to pain when needles were thrust into the witch's mark.[5] Cicatrization could account in a large measure for this phenomenon, but, considering the brutal nature and concomitant panic of the trials, hysteric hyperanesthesia might equally serve, to say nothing of the possible narcotic effect of various witches' potions and ungents. It is curious, to cite one more instance of the probability of simple observation, that skeptics who debunk the mediaeval miracle of bleeding hosts by pointing in triumph to *micrococcus prodigiosus,* overlook the fact that on the darker side of miracle this frequently appears too as a common accusation against witches, supposedly, in accordance with commonplace homeopathic magic, the result of torturing hosts. For the miracle an appeal is made to science, but for the superstition of witchcraft only torture is argued.

All these pale, however, before the repeated confessions of flying to the sabbat [6] and indulging in wild dance and sexual orgies. Surely here, it is argued, *only* ignorance and torture can account for this oft

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Von Bardeleben's (Verhandl. d. anatom. Gesellschaft, 1892) observation of 906 cases of polymastia out of 6437 examinations of military conscripts. For distribution (and a striking parallel to renaissance observations) they cite Hartnung (Inaugural Dissertation, Erlangen, 1872) who found the following loci in 29 cases (female): 18 on breast, 2 in the axilla, 1 in the axillary line, 2 above the umbilicus, 1 on the thigh, 1 on the back, 3 on the groin, 1 on the vulva. The anthropologist, Klaatsch, in his *The Evolution and Progress of Mankind* (tr. by J. McCabe), London, 1923, maintains that there is usually at least one additional breast, above the real breast, even in the case of European women, giving milk rarely and having no nipple, which can almost always be detected on the breast of a well-formed woman.

5. Quite aside from polymastia (as well as birthmarks, hemorrhoids, warts, and other malformations a credulous examiner might consider an extra teat) an initiatory mark was frequently part of the witch ritual, probably deriving from the primitive custom of rubbing matter into holes pricked in the skin or inserting mud under the skin until a ridge is raised in the required pattern. If cicatrization were practiced as well, insensitivity as well as freedom from bleeding might result. Cf. Hughes, *op. cit.,* p. 88.

6. Cf. Guazzo, *Compendium Maleficarum,* Milan, 1608; Sprenger and Kramer, *Malleus Maleficarum,* Frankfort, 1582; for the best known of the renaissance treatises for accounts of the standard operating procedure. Also in Hansen's *Quellen und Untersuchungen zur Geschichte des Hexanwahns,* Bonn, 1901, and Lea's *Materials Toward a History of Witchcraft,* 3 vols., U. of Penn., 1931. Good short accounts of the sabbat may be found in Murray (*op. cit.*); Summers, *The History of Witchcraft and Demonology,* N. Y., 1926; Wickwar's *Witchcraft and Black Magic,* London, n.d., and Michelet's *Satanism and Witchcraft* (tr. A. R. Allenson) N. Y., 1939.

confessed cliché of demonic worship. Such an assumption can be made only by disregarding completely the pharmaceutical aspects of the witches' ointment.[7] While the sexual practices of the sabbat with their long line of descent from ancient fertility cult rites have already received considerable attention [8] and indeed in the renaissance texts on the subject are easily the most emphasized aspect of the scandalous behavior of witches,[9] there has been insufficient attention to the connection between the use of aconite and atropine at the sabbat, indicating a distinct cause and effect relationship which explains some facts of the witch's confession with far greater plausibility than the usual allusion to torture.

To be sure the delerifacient effects of *atropa belladonna* alone could account for any bizarre confession on the part of the user, but what is strikingly pertinent is the consistent confession of flying to the sabbat, coupled with abandoned (and frequently apodysiac) dancing.[10]

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7. The "flying ointment," deriving ultimately no doubt from ancient ceremonial uses of oil, while frequently containing such dramatic elements as baby's fat and such mundane ingredients as soot and parsley, certainly involved monkshood, deadly nightshade, and henbane. Some authorities include Jimson weed. The three major alkaloids definitely used in these ointments then are: aconitine ($C_{34}H_{47}NO_{11}$) from *aconitum napellus* (monkshood); atrophine ($C_{17}H_{23}NO_3$) from *atropa belladonna* (deadly nightshade); and hyoscyamine ($C_{17}H_{23}NO_3$) from *hyoscyamus niger* (henbane). If Jimson weed (Datura stramonium) is included we may add scopolamine ($C_{17}H_{21}NO_4$). Any question of the toxicological effect of these ingredients used as a salve (as against the indubitable results taken internally) must take into consideration that the ointment was mostly applied to the legs and the vaginal membranes which could convey the toxins to the blood stream. Further it should be borne in mind that the louse-bitten skin of a witch was unlikely to be unbroken. Gonzales, Vance, Helpern, and Umberger in *Legal Medicine, Pathology, and Toxicology*, N. Y., 1954 (2d ed.) p. 852, report poisoning from the application of belladonna plaster to the skin. Glaistner (*Medical Jurisprudence and Toxicology*, Edinburgh, 1953 (9th ed.) p. 650), states more generally that the use of belladonna as an external application in the form of liniament and plaster and as an enema has caused serious and even fatal results. He reports toxic symptoms after the use of a two-grain pessary.

8. Murray (*op. cit.*), Hughes (*op. cit.*), Summers (*op. cit.*), and many others.

9. Boguet, *Discours de Sorciers*, Lyons, 1590, Bodin, *De la demonomanie*, Paris, 1580, in particular, although most 16th and 17th century texts on the subject contain lengthy treatments of the sexual orgies. Sodomy, pederasty, incest, and homosexuality are commonly reported. Guazzo's *Compendium Maleficarum* contains woodcuts illustrating amongst other things the ritual anal kiss of the sabbat (the notorious *osculum infame* charged against the Waldenses and the Templars).

10. Quite apart from the formal back-to-back dance ceremony.

Now aconite produces amongst other effects an irregular heart action. The sensation of falling is frequently associated with this type of cardiac irregularity. Such a reaction coupled with the delerifacient action of belladonna (and note that both drugs were commonly used) might well account for the consistent confession of flying [11] on the part of witches as a result of bona fide experienced sensation as well as the belief in itself. Indeed the belief, followed by the effect of the drugs, easily, in my opinion, accounts for the oft-noted sincerity of the confessions; the belief a delusion, but the drugged experience real.

Far more curious, however, in the reported effects of *atropa belladonna* is its possible role in the frenzied dance behavior of sabbat participants so widely confessed by the witches and stated by those who secretly observed the rites. Gonzales, Vance, Helfern, and Umberger [12] state on *atropa belladonna:* "Poisoning by atropine and its related alkaloids causes such symptoms as dryness of the throat, dysphagia, huskiness of the voice, dilated pupils, impaired vision, hallucinations, giddiness, delirium, excitement, *choreiform movements* (my italics), and convulsions."

Hallucinations, delirium, and choreiform movements; [13] it is a little ironical to find the clinic of the twentieth century giving some credence to the impossible confessions of the sixteenth.

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11. Dr. A. J. Clark in his appendix to Murray (*op. cit.*) was the first to advance this hypothesis.

12. *Op. cit.*, pp. 852-53.

13. A German toxicologist, Gustav Schenk, in *The Book of Poisons*, (tr. M. Bullock) N. Y., 1955, pp. 36-37, who also reports the dancing symptom, is even more suggestive as to the *mental condition* of participants in the sabbat when he says (in describing effects of *atropa belladonna*): "At the climax of this mood of exhilaration, his excitement grows more intense. *He is no longer master of his senses, which deceive him. He sees nonexistent figures and movements which no one makes. He hears music and sounds when there is complete silence all around him.* The colors of objects before his eyes change: green becomes black and a black surface appears to him a dazzling light. *His confusion grows greater and greater and in this phase he may easily be subordinated to another's will, for he is completely open to influence and will do whatever he is told.*" (My italics.) If Schenk is right, it is indeed a temptation to explain accordingly the docile behavior of initiates at sabbat ceremonies as well as the power of the cult leader to create such impressions as the real presence of Satan. The use of the artificial phallus to persuade women of actual intercourse with demons seems plausible indeed in terms of Schenk's symptoms. But this must remain mere speculation.

CLINICAL TRIALS OF MISCELLANEOUS AGENTS ON 271 CASES OF LYMPHOCYTIC LEUKEMIA

By John R. Sampey *

EARLIER studies have recorded more than 2500 cases of lymphocytic leukemia treated with radiophosphorus, nitrogen mustards, TEM, folic acid antagonists, 6-MP, urethan, ACTH and cortisone.[1] Scores of other antileukemic agents have been given clinical trials in the management of lymphoid leukemia. This paper presents 93 published reports on such agents since 1949.

Table 1 tabulates the results with the five agents which have been tested on the largest number of patients. The remission rates were obtained by considering only those reports which tabulated both the number of cases treated and the number responding.

While the number of cases treated with miscellaneous agents is too limited for evaluation of the therapy the investigations do serve to indicate those which merit further clinical trials.

TABLE I

MISCELLANEOUS AGENTS AND LYMPHOID LEUKEMIA

Agents	Refs.	Cases	Acute	Chronic	Remissions	Reports Not Stating Rem.	Remission Rate
Phosphoramides	9	29	3	26	23	1	79%
Colchicines	14	27	4	23	7	4	30%
Transfusions	7	27	6	21	9	2	73%
Radioisotopes	5	21	8	13	11	1	52%
Myleran	4	16	—	16	5	1	31%

The original literature was made available by the National Library of Medicine, and the libraries of Furman University and Greenville General Hospital.

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TABLE II

MANAGEMENT OF LYMPHOID LEUKEMIA WITH MISCELLANEOUS AGENTS

Cases	*Acute*	*Chronic*	*Remissions*	*Comments on Therapy*	*References*
7	2	5	5	Colcemid. Good clinical and hematologic remissions in 5 chronic cases. No effect in subacute.	Polli 1955
5	—	5	—	Colcemid. Little effect.	Gigante 1955
4	—	4	1	Demecolcin. Good remission for 6 months.	Storti 1954(1)
4	—	4	—	Substance F. Best rem. with H. D. and lym. leuk.	Storti 1954(2)
1	—	1	—	Colcemid. Aggravated condition.	Leonard 1955
2	—	2	—	Demecolcin. No effect.	Leonardi 1954
2	1	1	1	Demecolcin. Subjective improvement in chronic, no effect in subacute case.	Moeschlin 1953
1	—	1	—	Colcemid. No effect.	Volterra 1955
1	1	—	—	Colcemid. No improvement.	Alexandrides 1957
—	—	—	—	Demecolcin. Variable response.	Bock 1954
—	—	—	—	Colchicine. No results.	Ceresa 1954
—	—	—	—	Colchicine. No effect in acute cases.	Grant 1954
—	—	—	—	Colchicine and As. Some rem. in 35 chronic cases.	Kolar 1952(1)
—	—	—	—	Colchicine and nitrogen mustards. Used as complements to radiotherapy.	Kolar 1952(2)
8	—	8	6	Phosphoramides. Good clin., hemat. remissions.	Leonard 1956
7	—	7	5	Phosphoramides. Good clin., hemat. remissions.	Shay 1953
5	—	5	5	Phosphoramides. Some hemat. rem. to 2.5 months.	Winkler 1956
2	—	2	2	Phosphoramides. Clin. and/or hemat. remissions.	Zarafonetis 1955
—	—	—	—	Phosphoramides. Good remissions.	Hunter 1956
2	2	—	1	Phosphoramides. Brief hemat. remission.	Paterson 1951
1	1	—	1	Phosphoramides. Fair remission.	Paterson 1953
3	—	3	2	Phosphoramides. Fair objective response.	Sykes 1953
1	—	1	1	Phosphoramides. Clinical rem. of 5 weeks.	Sykes 1956
8	—	8	—	Myleran and TEM. Slower response than in myeloid.	Marmont 1954
6	—	6	5	Myleran. 2 very good and 1 good remission.	Klima 1953
2	—	2	—	Myleran. No response.	Wagner 1954
—	—	—	—	Myleran. No effect in chronic or acute.	Wintrobe 1954
3	—	3	—	Antibiotics. No response.	Field 1957
2	—	2	—	Antibiotics. No response.	Kasdorf 1954
1	—	1	—	Antibiotics. Little response.	Friedman 1952
1	—	—	1	Antibiotics. Clin. response only in leuk. of skin.	Keller 1952

Cases	*Acute*	*Chronic*	*Remissions*	*Comments on Therapy*	*References*
1	—	—	1	Antibiotics. Good rem. in cutaneous leukemia.	Miescher 1951
—	—	—	—	Antibiotics, x-rays and percoten. 1 survival for 4 years, and several 1 to 2 years for chronic cases.	Mikhriloff 1954
—	—	—	—	Antibiotics, x-rays. Fair rem. in chronic cases.	Magnus 1955
—	—	—	—	Antibiotics, transfusions. Longer survival.	Bierman 1950
10	10	—	10	Infections. 2 rem. with hemolytic staphyloccus septicemia, 1 varicella, 1 feline panleukopenia, and less complete rems. with 6 other cases.	Bierman 1953
1	—	—	1	Infections. Rapid improvement following polio.	Herrbach 1955
1	—	—	1	Infections. Clin. rem. with West Nile and Ilheus virus infections.	Southam 1951
7	7	—	2	Proteinamine. Remissions.	Brennan 1951
4	4	—	4	Thymectomy. Short-lived improvement.	Dean 1951
1	—	1	1	Insulin/glucose. Both induced brief hemat. rem.	Gitman 1951
2	—	2	—	Glucosamine. No effect.	Marlow 1953
5	—	5	—	Androgens, estrogens. Brief hemat. remissions.	Storti 1951
3	—	3	3	Progesterone. 2 objective, 1 subjective rem.	Villa 1955
2	—	2	1	Hormone HBF386. Good remission.	Meythaler 1952
6	—	6	5	Splenectomy. 4 prolonged, 1 brief remission.	Fisher 1951
6	—	6	6	Splenectomy. 4 prolonged, 2 brief remissions.	Fisher 1952
2	—	2	2	Splenectomy. 1 good rem. 2 yrs., 1 fair 1 month.	Hunter 1950
3	—	3	2	Thiouracil. Good hematic remissions.	Bernard 1952
1	—	—	—	Thiouracil. Increased leukocyte count.	Valdes 1952
1	—	1	1	Sulfapyridine. Leukocyte count lowered briefly.	Bichel 1950
4	—	4	2	Urethan, thiouracil. Fair response to combination.	Olmer 1954
2	2	—	—	Sulfate, S^{35}. No improvement.	Ellis 1955
6	—	6	3	Benzene. Marked fall in leukocyte count.	Braier 1953
5	—	5	3	Au198. 1 good, 2 fair hemat. remissions.	Fellinger 1955
—	—	—	—	Au198, Bi206. Good rem. on chronic cases.	Van Werff 1955
2	2	—	2	Bi206. Complete clin. and hemat. remissions.	Van Werff 1956
8	4	4	4	As76. 1 chronic had good rem., 3 subacute fair rem.	Block 1949
6	2	4	2	As76. 1 rem. of 5 mos. in chronic, 1 clin., hem. rem. in acute case.	Block 1953
1	—	1	1	Arsenite. Good clin., hemat. remission.	Florijn 1950
12	—	12	—	Transfusions. Some partial clin., hemat. rems.	Vakar 1955
9	—	9	5	Transfusions. Good remissions.	Schulz 1956
1	1	—	1	Transfusions. Fair rem. in a child.	Piney 1950
3	3	—	1	Transfusions. Clin., hemat. rem. in an adult.	Henstell 1949

Cases	*Acute*	*Chronic*	*Remissions*	*Comments on Therapy*	*References*
1	1	—	1	Transfusions. Complete rem. for 5 weeks.	Tousek 1955
1	1	—	1	Transfusions, vitamin B_6, penicillin. Complete rem.	Lombos 1949
—	—	—	—	Transfusions. 50% favorable response in chronic.	Schoyer 1956
2	—	—	*2*	Chloramphenicol. Almost complete remissions.	Macciotta 1953
1	1	—	1	Chloroamphenicol. Remission for 1 month.	Lonati 1950
4	4	—	4	Glycolytic enzyme inhibitors. 3 good, 1 fair objective rem., 3 good, 1 poor subjective rem.	Black 1949
—	—	—	—	Proteolytic enzymes. Promising in lym., myl. leukemias.	Gaschler 1955
7	—	*7*	*7*	Ganglionic, medullary fractions. Good response.	Tremblay 1954
2	—	—	*2*	Bone marrow extracts. Clin., hemat. remissions.	Poumailloux 1954
—	—	—	—	Bone marrow extracts, transfusions, ACTH. Good clin. and hemat. rem. in acute lymphoid, myeloid leukemias.	Tremblay 1953
4	4	—	*3*	Desoxypyridoxine. Brief response in adults.	Weir 1954
3	—	—	—	O_2 inhalation. Hemat. remissions.	Cocchi 1954
—	—	—	—	Thoron inhalation, x-rays. Some rem. in both chronic lymphoid and myeloid leukemias.	Cluzet 1953
1	—	1	—	Azaguanine. No change in blood picture.	Colsky 1955
4	4	—	*2*	Vitamin B_{12}. Partial rem. for less than 5 months.	Welsh 1952
1	—	1	1	Calciferol. Good rem. for 18 months.	Pirila 1952
1	—	1	1	Ethylenimine of picric acid. Some remission.	DiPietro 1952
—	—	—	—	Choline. Furthers effects of x-rays, urethan, etc.	Gansslen 1950
1	1	—	1	Alpha peltation. Brief remission.	Greenspan 1954
1	—	—	1	Butalidon. Palliative.	Jeschal 1956
1	—	1	—	p-Aminobenzoic acid. Preliminary results.	Kelemen 1949
2	—	*2*	*2*	Yeasts. Clinical response.	Protti 1955
1	1	—	1	AF2. Partial remission.	Schwerdtfeger 1950
1	1	—	—	Folic acid. Anaphylic shock suffered.	Rausch 1956
1	—	—	1	Naphthylamine. Good remission.	Spigliati 1951
1	1	—	1	Myelokeutric acid. Extract from urine of patient with chronic myeloid leuk. gave hemat. remission.	Swann 1950

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SELECTED ABSTRACTS

Ionic Incompatibilities in Prescriptions. Bruin, V. H., and Oliver, W. H. *Austral. J. Pharm. 38:226* (1957). The authors stated that ionic incompatibilities in prescriptions are often not given as much consideration as they should be. They indicated, for example, that the precipitation of insoluble inorganic acids from solutions of their soluble salts is usually considered solely on the basis of the pH. However, admixture of these acids with solutions of cations of weak bases is a frequent source of precipitation reactions, even at a pH where the parent acid or base would not be precipitated.

The authors tabulated the results obtained from mixtures of salts of weak acids and salts of weak bases. With sodium phenobarbital, magnesium sulfate caused crystals to form at a pH of 9.3 when the equimolar concentrations were M/5 or greater. Likewise, with sodium phenobarbital, calcium chloride caused crystals to form at a pH of 9.2 when the equimolar concentrations were M/10 or greater. Since, at this high pH, the solubility of phenobarbital exceeds the M/5 concentration present, the precipitates could not be phenobarbital. Also, analyses of the crystals demonstrated the presence of magnesium and calcium, respectively.

With sodium phenobarbital, precipitates were formed with codeine phosphate at a pH of 7.0 and an equimolar concentration of M/100 or greater and with Benadryl at a pH of 7.9 and an equimolar concentration of M/80. Based upon the solubility of phenobarbital with respect to pH, the authors concluded that codeine phenobarbital and diphenhydramine phenobarbital were formed.

Sodium sulfathiazole, being the salt of a weak acid, was mixed with magnesium sulfate and calcium chloride in equimolar concentrations. Crystals formed at a pH of 9.6 and a concentration of M/10 with magnesium sulfate and at a pH of 9.2 and a concentration of M/5 with calcium chloride. Since the solubility of sulfathiazole was greater than that present at the pH used, the authors concluded that the magnesium and calcium salts, respectively, of sulfathiazole had precipitated.

Equimolar mixtures of potassium iodide with Benadryl and codeine phosphate were also studied. At a concentration of M/30 and a pH of 7.0, crystals were formed with Benadryl and at a con-

contration of M/30 and a pH of 4.6 crystals were formed with codeine phosphate. On standing for several months, the solutions containing codeine phosphate and potassium iodide deposited reddish brown crystals of codeine periodide.

The authors concluded that the results of this short study indicate that pH is not the only factor to be considered in the study of ionic incompatibilities. They emphasized that many of the precipitates were slow in forming, sometimes requiring several weeks. They advised that, in the absence of sufficient time for testing, aqueous mixtures containing both salts of a weak acid and a weak base be assumed to be incompatible.

Errors in Dispensing Medicines. Capper, K. R., and Dare, J. G. *The Chemist and Druggist 168:297* (1957). The authors reviewed work performed over recent years, some under their direction and some under the direction of others, in an attempt to provide "information which will enable pharmacists to decide whether the limits now generally applied reflect quantitatively what can be reasonably regarded as the accuracy acceptable as sound pharmaceutical practice in dispensing mixtures and other liquid medicines."

Under experimental conditions it was found that a difference of 1/125 in. in the rise or fall of water in a pharmaceutical measure could be discerned. However, for dispensing purposes, this was considered to be an accuracy greater than could be expected. Therefore, a 1/100 in. standard deviation in sighting error was considered to be reasonable. Consequently, a 1/40 in. sighting error should include 99 out of 100 measurements. Based upon a 1/40 in. error, a 30 minims measurement in a graduate having a diameter of ½ in. would have an error of 1.36 minims or 4.5 per cent. Larger volumes would normally show a smaller percentage error since the diameter of the graduate would not increase in direct proportion to the volume. This was borne out in data reported. Another error likely to contribute to sighting errors is the dark line resulting from internal reflection which may be confused with the foot of the meniscus. This error is always negative and was reported as being about —6 per cent at a 60 minims measurement. Other measurement errors noted by the authors were the problem of seeing the foot of the meniscus in deeply colored or opaque liquids, residues remaining in graduates upon transfer, and the use of bottles as measures.

Variations in dispensing solids depend on the accuracy of the balance and weights and on losses in transferring the solid. Data presented on the latter loss showed, for example, that 3 per cent of 1 grain of calomel was lost when transferred from the balance pan and 12 per cent when transferred from a weighing paper. With 10 grains of calomel the loss was 1.5 and 1.6 per cent, respectively.

In the making and using of stock solutions, the authors pointed out that the errors due to volume measurement are likely to be greater than those due to weighing. Since these stock solutions are used as a measured volume, two errors in volume measurement are apt to be introduced. Therefore, the use of stock solutions to obtain a quantity of a solid is apt to produce considerable variation in accuracy.

In a study involving controlled conditions, seven pharmacists dispensed several simple prescriptions using seven sets of equipment. Each prescription was dispensed 49 times. Each pharmacist used every piece of equipment during the study. An analysis of the factors contributing to the variations in accuracy obtained revealed that neither the differences between balances nor measures were statistically significant, but the personal errors of the pharmacists differed significantly. It was also found that the direction (positive or negative) and magnitude of the personal errors for each pharmacist was quite consistent, apparently a characteristic of his dispensing. It was found, also, that dispensing under the strain of high speed requirements resulted in significantly larger personal errors. Further experiments also showed that measuring volumes with the graduate in hand resulted in significantly larger errors than when it was placed on a counter.

The authors pointed out that there are three procedures for determining the magnitude of variation in dispensing. One is the synthetic process, in which each likely source of error, as sighting error, equipment calibration error and personal error, is evaluated and the likely magnitude of variation combined. Such an approach produces an exaggerated error since all of the individual errors will not likely operate in the same direction at once. The second procedure is an examination of the results obtained when medicines dispensed under controlled laboratory conditions are analyzed. The third is an examination of results obtained when medicines dispensed in general practice are analysed. The latter procedure, in isolation, cannot give data which will provide a basis for the determination of what degree of variation is reasonable since no information is available about the

dispensing method used. Although the evidence from any one of these three procedures is not adequate for a final assessment of error, in so far as the results from the three methods confirm each other, an estimate of reasonable limits of variation can be reached.

The Absorption of Sulfadiazine From an Emulsion Vehicle. May, C. N., and Hassler, W. H. *The Bull. Am. Soc. Hosp. Pharm. 14:*419 (1957). The absorption of sulfadiazine from a tablet, a suspension, and from an emulsion was compared by administering the same total amount of sulfadiazine in each of the three forms to each of 14 volunteers. The sulfadiazine was administered in a dose of 5 Gm. (divided) a week apart, the tablet being given the first week, the emulsion the second, and the suspension the third week. Eleven hours following the dose of the sulfonamide a blood sample was taken by venipuncture and the amount of sulfadiazine in the plasma determined. The urinary excretion was also determined during three twelve hour periods following the administration of the drug.

The results obtained showed that the average plasma level was 8.5 mg. per cent following the emulsion, 6.07 mg. per cent following the suspension, and 5.0 mg. per cent following the tablets. The average total urinary secretion from 10 subjects during the 36 hours of the test was 3.23 Gm. following the emulsion, 2.53 Gm. following the suspension, and 1.04 Gm. following the tablets. Thus, the emulsion provided greater sulfadiazine absorption than either the tablets or the suspension. The differences were found to be statistically significant.

The authors also found that the sulfadiazine emulsion was stable during a shelf life of more than six months. The emulsion was prepared in a colloid mill and had the following formula:

Sulfadiazine powder	200 Gm.
Wesson Oil (hydrogenated cottonseed oil)	500 ml.
Polyoxyethylene sorbitan monostearate	36 ml.
Sorbitan monooleate	84 ml.
Sodium saccharin	0.4 Gm.
Sodium benzoate	2.0 Gm.
Imitation vanilla conc.	3.3 ml.
Distilled water, q.s., ad.	1000.0 ml.

A Test for the Effect of Fluorides on the Solubility of Tooth Enamel. Gershon, S. D., Neiditch, O. W., and Lee, R. H. C. *Drug and Cosm. Ind. 82*:160 (1958). The authors developed and described a test for the solubility of powdered tooth enamel before and after treatment with fluoride solutions. The development of the method was directed particularly toward the removal of reagent precipitates and reaction products prior to the determination of solubility.

The results obtained from the use of the test method confirmed other reports that the application of fluorides to tooth enamel reduced its solubility in acid. The results also indicated that the reduction of enamel solubility was dependent on the concentration and pH of the fluoride solution. Buffered fluoride solutions were more effective in reducing enamel solubility than unbuffered solutions. At pH levels between 3 and 9, sodium fluoride was slightly more effective than stannous fluoride, but below 3 a sharp increase in the effectiveness of stannous fluoride in reducing the solubility of enamel in acid was observed while the protective activity of sodium fluoride showed little increase. In comparison with unbuffered solutions of the same pH range, sodium fluoride solutions buffered between a pH of 3 and 7.25 were more effective than the unbuffered solutions in reducing enamel solubility.

The results from this test also showed that increasing the fluoride content of buffered sodium fluoride solutions from about 10 ppm F^- up to 500 ppm increased the resistance of the enamel to solution in acid. Repeated decalcification of enamel treated with sodium or stannous fluoride solutions, buffered at a pH of 4.0 and having a fluoride content of 250 ppm, showed that the sodium fluoride treated enamel was much superior to stannous fluoride treated enamel in resisting repeated decalcification attacks.

The authors also pointed out that sodium fluoride solutions adjusted to pH 4 with hydrochloric acid attacked tooth enamel. Phosphate buffered sodium fluoride solutions adjusted to a pH of 4 showed less tendency to attack enamel.

The authors indicated that the significance of the findings reported would not be evident until adequate correlation had been established with clinical studies. However, it was felt that the findings indicated that further studies were in order to determine the acceptability for topical application of 0.5M phosphate buffered sodium fluoride solutions at pH 4.

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